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(54) N-Acyl-2,3-benzodiazepine derivatives, pharmaceutical compositions containing them and process for preparing same.

(57) The invention relates to novel N-acyl-2,3-benzodiezapine derivatives of the general formula (I), their stereoisomers and acid-addition salts, pharmaceutical compositions containing them and a process for their preparation. In the general formula (I)

R — stands for a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;

R^1 — means hydrogen; or R^1 is absent when a double bond exists between the N(3) and C(4) atoms;

R^2 — means a C_{1-3} alkyl group; or

R^1 and R^2 — together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;

R^3 — means hydrogen or a C_{1-4} aliphatic acyl group;

R^4 — represents hydrogen; a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; and

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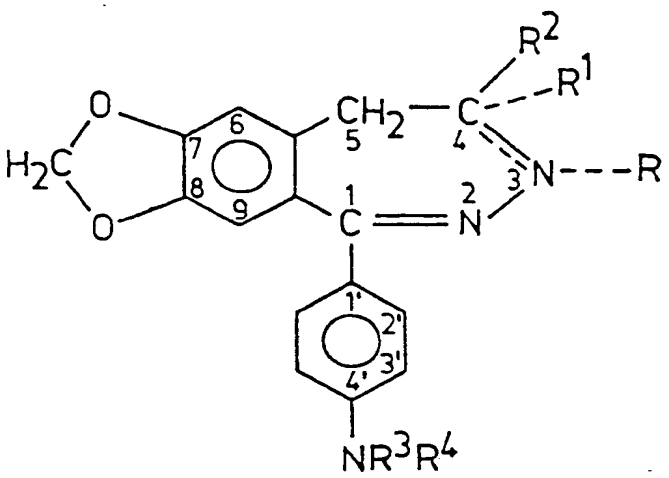
the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R^3 and R^4 stand for hydrogen.

The compounds of the general formula (I) possess valuable central nervous system effects, particularly muscle-relaxant, anticonvulsive and neuroprotective action. Thus, they may be useful for the treatment of various diseases of central nervous system origin.

This invention relates to novel N-acyl-2,3-benzodiazepine derivatives of the general formula (I)



(I)

wherein

R stands for a C_{1-6} aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;

R^1 means hydrogen; or R^1 is absent when a double bond exists between the N(3) and C(4) atoms;

R^2 means a C_{1-3} alkyl group; or

R^1 and R^2 together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;

R^3 means hydrogen or a C_{1-4} aliphatic acyl group;

R^4 represents hydrogen; a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R^3 and R^4 stand for hydrogen,

and their stereoisomers as well as acid addition salts (where possible) and pharmaceutical compositions containing these compounds.

As number of carbon atoms in the respective groups 1 to 4 (so far as not anyhow the upper limit is 4), particularly 1 or 2, is preferred. From the halogen atoms fluorine and chlorine are preferred. In case of fluorine atoms preferably 3 of them are present as substituents.

The compounds of general formula (I) according to the invention have an asymmetric molecular structure. The general formula (I) relates to all possible individual stereoisomers and their mixtures.

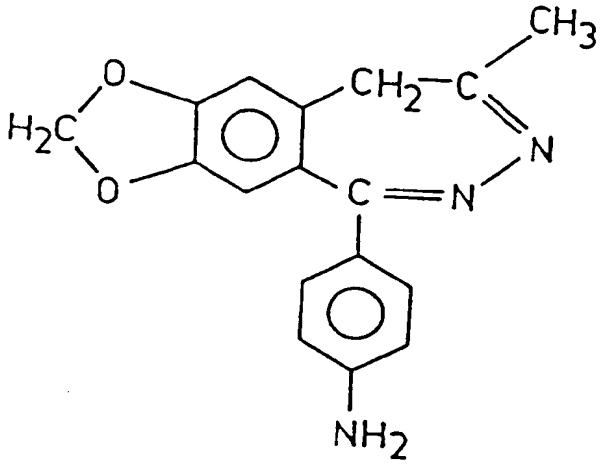
According to an other aspect of the invention, there is provided a process for the preparation of the new compounds of general formula (I) and the acid-addition salts thereof.

The aim of the present invention is to develop new compounds of the general formula (I) which possess valuable central nervous system (CNS), particularly muscle-relaxant and/or anticonvulsive, activity. A single compound showing such effect is only known among 2,3-benzodiazepines, namely 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine(United States patent specification No. 4,614,740) also prepared by the authors of the present invention. In the course of detailed pharmacological screening it was revealed, however, that the above compound was positive in the Ames-test, i.e. it proved to be mutagenic. Thus, it is the specific aim of the present invention to find out novel 2,3-benzodiazepine derivatives which retain their valuable muscle-relaxant and anticonvulsive activity but are negative in the Ames test.

The new compounds of general formula (I), wherein R, R^1, R^2, R^3, R^4 and the dotted lines are as defined above, and their pharmaceutically acceptable acid-addition salts completely satisfy this requirement.

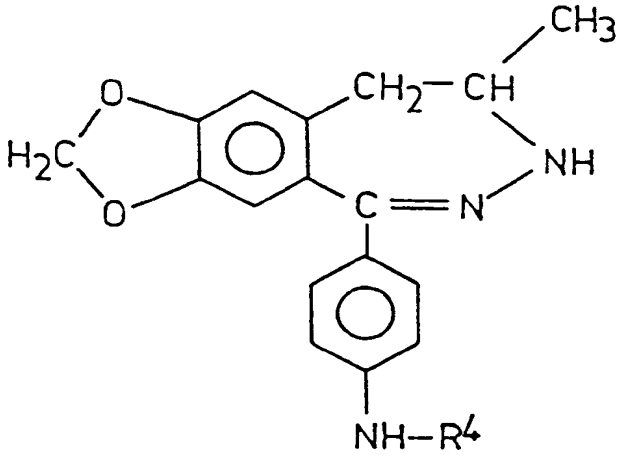
According to the invention, the compounds of general formula (I) are prepared by

a) acylating a compound of formula (II)



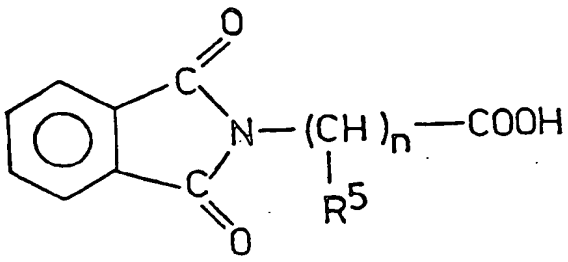
(II)

with a C_{1-6} aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R^4 means a C_{1-6} aliphatic acyl group substituted by a halogen, with a C_{1-4} alkylamine, di(C_{1-4} alkyl)amine or pyrrolidine,
to obtain compounds of the general formula (I), wherein R^2, R^3 and the dotted lines are as defined above, R^4 means a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxy, phenyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R^1 are absent and a double bond is present between the N(3) and C(4) atoms;
b) acylating a compound of the general formula (III),



(III)

wherein R^4 is as defined above, with a C_{1-6} aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R^4 means a C_{1-6} aliphatic acyl group substituted by a halogen, with a C_{1-4} alkylamine, di(C_{1-4} alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R^1, R^2, R^3, R^4 and the dotted lines are as defined above, R means a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxy, phenyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or
c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),



(VI)

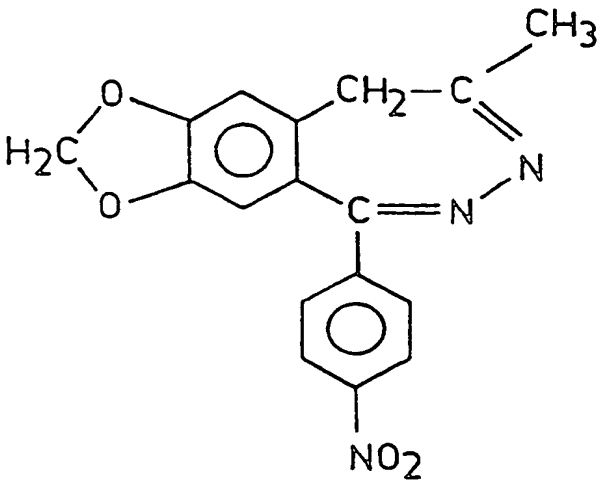
wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 stands for a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group, both R and R^1 are absent, and a double bond is present between the N(3) and C(4) atoms; or

d) acylating a compound of the general formula (III), wherein R^4 is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 is as defined above except hydrogen, R stands for a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

e) reacting a compound of the formula (II) with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 represents a C_{1-5} alkylcarbamoyl or phenylcarbamoyl group, R and R^1 are absent and a double bond is present between the N(3) and C(4) atoms; or

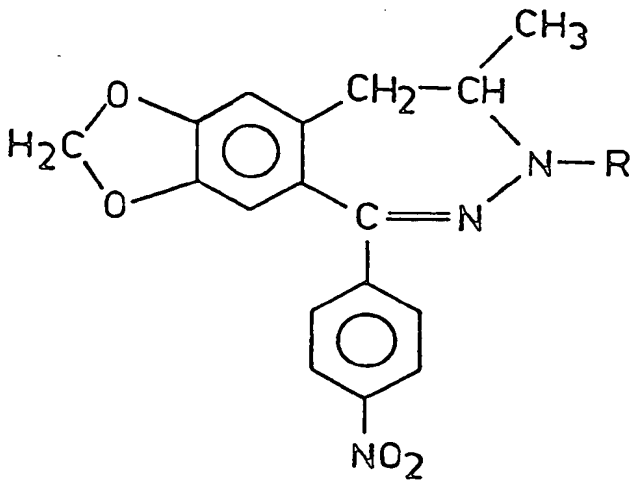
f) reacting a compound of the general formula (III), wherein R^4 is defined as above, with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 is as defined above except hydrogen, R stands for a C_{1-5} alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

g) selectively reducing a nitro compound of the formula (IV)



(IV)

to a novel compound of the general formula (V)



(V)

wherein R means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein R is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein R^4 stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein R^1, R^3 and R^4 represent hydrogen, R^2, R and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

h) acylating a new compound of the general formula (I), wherein R, R^1, R^2 and the dotted lines are as defined above, R^3 and R^4 mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C_{1-6} aliphatic carboxylic acid optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative thereof, to obtain compounds of the general formula (I), wherein R^1, R^2, R^3 and the dotted lines are as defined above, R and R^4 represent a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N-(3) and C(4) atoms; or

i) reacting a new compound of the general formula (I), wherein R, R^1, R^2 and the dotted lines are as defined above, R^3 and R^4 mean hydrogen and no double bond is pesent between the N(3) and C(4) atoms, with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R stands for a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; R^3 stands for hydrogen; R^4 represents a C_{1-5} alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

j) acylating a new compound of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 and R^4 mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R represents a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group; R^3 stands for hydrogen, R^4 represents a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

According to a preferred embodiment of the process of the present invention the acylation of the compounds of the general formulae (I), (II), (III) and (V) can be carried out preferably with a suitable carboxylic acid, in the presence of dicyclohexyl-carbodiimide in a suitable solvent, preferably in dichloromethane, in a temperature range of 10 to 30 °C during 1 to 25 hours.

According to an other preferred embodiment of the present invention the compounds of the general formulae (I), (II), (III) and (V) can be acylated in a temperature range of zero to 150 °C by a suitable

reactive acyl derivative, i.e. carboxylic acid anhydride, mixed anhydride or acyl chloride, in the absence or presence of a solvent usually applied in acylations of such types such as chloroform or dichloromethane, in the absence or presence of an acid-binding agent, such as triethylamine. If the additive acylation is performed with isocyanates, the reaction is advantageously carried out in dimethylformamide, benzene or dichloromethane in a temperature range of 15 to 100 °C during 0.5 to 100 hours.

The selective reduction of the compound of general formula (IV) to the compound of general formula (V), wherein R denotes a hydrogen atom, can be performed by an inorgaic or inorganic-organic complex metal hydride, preferably sodium borohydride, in a solvent or solvent mixture which has no or only low reactivity to the complex metal hydride applied. In these reactions a C_{1-4} alcohol or pyridine is the solvent of choice. (Similar selective reductions are described in the U.S. patent specifications Nos. 4,423,044 and 4,835,152.)

The nitro group of the new compounds of general formula (V) are reduced to an amino group by hydrazine or hydrazine hydrate in the presence of a catalyst such as palladium, platinum or Raney nickel in a C_{1-4} alcohol, dioxane, tetrahydrofuran, benzene, dimethylformamide, dimethylacetamide or in a mixture thereof.

According to a preferred embodiment of the process of the present invention the reduction can be carried out in methanol by hydrazine or hydrazine hydrate in the presence of Raney nickel catalyst in a temperature range of 10 to 65 °C (U.S. patent specification No. 4,614,740) but, if desired, the reduction and the removal of the phthaloyl protecting group described in process d) can be performed in the same vessel.

The N-phthaloylamino acids of the general formula (IV) containing a chiral carbon atom, wherein R^5 means a C_{1-4} alkyl group and n is 1, can be prepared from DL-, L- and/or D-alpha-amino acids.

The compounds of the general formula (I) of the invention, which contain a basic amino group, wherein R^3 and R^4 mean a hydrogen atom or R and/or R^4 stand for an aminoacyl group, can be transformed to their acid-addition salts by known methods.

The preparation of the compounds of the general formula (II) used as starting materials in the process of the present invention is described in the U. S. patent specification No. 4,614,740, that of the compound of the general formula (III), wherein R^4 stands for a hydrogen atom, in the U. S. patent specification No. 4,835,152, while that of the compound of general formula (IV) is published in the French patent specification No. 85,09793. The compounds of general formula (III), wherein R^4 stands for various acyl grups, are new. The process for their preparation is described hereinafter, before Table 10, or they can be synthetized by methods described therein. The preparation of the new starting compounds of the general formula (V) is described in the Examples. The (α-ϵ)-amino acid derivatives of general formula (VI) are prepared by methods known from the literature [J. Am. Chem. Soc. 35, 1133 (1913); 41, 845 (1919); Berichte der Deutschen Chemischen Gesellschaft 40, 498, 2649 (1907); 46, 1103, 3159 (1913); 47, 3166 (1914)] or by known methods using the reaction of phthalimide potassium with the required halocarboxylic acid.

The compounds of the general formula (I) prepared by the process of the present invention possess central nervous system (CNS) activity, such as anticonvulsive, muscle-relaxant and neuroprotective effects, which can be shown by pharmacological tests.

In the comparative study 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (U. S. patent specification No. 4,614,740, in the following "reference compound"), having similar structure and efficacy as the compounds of the invention, was applied as reference compound. As already mentioned in the introduction, this compound proved to be Ames-positive in addition to its valuable pharmacological properties. In opposition to this the compounds of the present invention proved to be negative in the Ames-test.

The pharmacological effects of the compounds of general formula (I) are presented in Tables 1 to 8.

Narcosis-potentiating effect in mice

The narcosis-potentiating effect was tested with 3 oral doses in 10 mice/dose. The ED_{50} value is the dose prolonging the narcosis period induced by 50 mg/kg of i.v. sodium hexobarbital to its twofold value in 50 % of the animals in comparison to the control group treated only with the vehicle. The ED_{50} values were calculated by the Litchfield-Wilcoxon method [J. Pharmacol. Exp. Ther. 96, 99 (1949)]. The results are presented in Table 1.

Table 1

Narcosis potentiating effect in mice

Compound Example No.	ED_{50} p.o. mg/kg
Reference compound	7.4
15 (16)	3.6
18	8.8
39	27.5
42	7.9
44	13.5

Table 1 (contd.)

Compound Example No.	ED_{50} p.o. mg/kg
44	13.5
45	4.9
46	11.5
48	5-8
49	9.5
56	12.5-25
60	4.4
62	5.2
66	24.0
69	15-20
73	4.5
98	5.8
107	6.25-12.5
108	≈ 12.5
109	≈ 12.5
115	7.7

The data of Table 1 demonstrate that the efficacy of several compounds is similar or significantly superior to that of the reference compound. Compounds of Examples 15 (16), 45, 60, 73 and 98 proved to

be especially potent.

Anticonvulsive effect in mic

The anticonvulsive effec of the compounds was measured by using the electroshock test [Swinyard: J. Pharmacol. Exp. Ther. 106, 319 (1952)], furthermore by using various chemical agents such as pentetrazole [Goodman: J. Pharmacol. Exp. Ther. 108, 168 (1953)], strychnine [Roskovski: J. Pharmacol. Exp. Ther. 129, 75 (1960)], bemegride, nicotine and 4-aminopyridine. The test compounds were orally administered in 3 doses, to 10 male CFLP mice per dose.

The results are presented in Table 2.

Table 2

Anticonvulsive effect in mice

Compound Example No.	ES	Pentetr-azole	Strychnine ED_{50} p.o. mg/kg	Bemegride	Nicotine	4-AP
Reference compound	38	115	87	73	70	43
15 (16)	12.5	37	>200	16	45	9
18	17.5	29				
39	53	170	>200	>200	>200	29
42	24	33	28	24	155	34
45	27	44	>100	51	30-80	≈70
46	20	57	>100	70-80	≈100	25-30
48	10.5	35-40				
49	25	53	>100	30-35	45	28
60	24	62				
62	12.5	56		25-50		
66	42	135	≈100	>100	100-150	84
69	57	>100				
73	16	62	50-100	49	53	25
98	8.4	19	20	11	19	13.5
107	23.5	120				
108	27	>100				
109	21	>100				
115	17.1	23.9				

ES = electroshock 4-AP = 4-aminopyridine

The above data demonstrate that the anticonvulsive effect of several test compounds (of Examples 15, 42, 45, 46, 73, 98, 107, 108, 109 and 115) is superior to that of the reference compound.

Muscle-relaxant activity in mice

The muscle-relaxant activity was measured in two tests. In Randall's inclined screen test [J. Pharmacol. Exp. Ther. 129, 163 (1960)] the compounds were applied in 3 i.p. doses to 10 CFLP mice per dose. The results are shown in Table 3.

Table 3

Inclined screen test in mice

Compound Example No.	ED_{50} i.p. mg/kg
Reference compound	47
15 (16)	23.5
18	31
42	42
45	35
48	20.5
49	36
60	150
62	25
66	52
73	27
98	18.0
107	>200
108	>200
109	61
115	16.1

The rotarod test was used to measure muscular tone and motor coordination [Dunham and Miya: J. Am. Pharm. Assoc. 46, 208 (1957)]. The results obtained with the three selected compounds of highest activity and that of the reference compound are presented in Table 4.

Tabl 4

Rotarod test in mice

Compound Example No.	ED_{50} i.p. mg/kg
Reference compound	24
15 (16)	3.7
42	8.1
98	8.6

Tables 3 and 4 demonstrate that several compounds possess strong muscle-relaxant activity (compounds of Examples 15, 18, 42, 45, 48, 49, 62, 73, 98 and 115).

Effect on spinal function

The effect on spinal function was studied with the most active compound (compound of Example 15 or 16) and the reference compound. Table 5 shows the effect on polysynaptic flexor reflexes in cats [Farkas and Kárpáti: Pharm. Res. Comm. 20, S1, 141 (1988)].

Table 5

Effect on spinal flexor reflex			
Compound Example No.	Cumulative doses mg/kg, i.v.	Inhibition of flexor reflex in per cent of control	ED_{50} mg/kg
Reference compound	0.25 0.5 1.0 2.0	12 30 57 77	0.90 (0.46-1.76)
15 (16)	0.05 0.1 0.2 0.4 0.8	11 19 31 52 77	(0.19-0.62)

The effect of the above compounds on the spinal root potentials in cats was tested in spinally immobilized animals [Farkas et al.: Neuropharmacology 21, 161 (1989)].

The results are presented in Table 6.

Table 6

Effect on spinal root potentials in cats					
Compound Example No.	Inhibition of reflexes in per cent of control				
	Cumulative i.v. doses mg/kg	Monosynaptic reflex	Polysynaptic reflex	Dorsal root reflex	Dorsal root potential
Reference compound	0.5	16	15	0	2
	1.0	27	24	2	4
	2.0	47	43	4	4
15 (16)	0.1	10	8	1	1
	0.2	10	16	3	2
	0.4	32	29	5	4
	0.8	56	51	11	8
	1.4	78	73	14	14

Monosynaptic reflex-inhibiting ED_{50} values:
Reference compound: 2.20 (1.02-4.75) mg/kg, i.v.
Compound No. 15 (16): 2.30 (1.06-5.01) mg/kg, i.v.
Polysynaptic reflex-inhibiting ED_{50} values:
Reference compound: 0.60 (0.32-1.13) mg/kg, i.v.
Compound No. 15 (16): 0.73 (0.39-1.37) mg/kg, i.v.

Electrophysiological tests

The inhibitory effects on the field potentials induced by electric stimulation in surviving rat neocortex slices in vitro [Fletcher et al., Br. J. Pharmacology 95, 585 (1988)] are summarized in Table 7.

Table 7

Inhibition of field potentials induced in rat neocortex slices			
Compound Example No.	Concentration µM	Inhibition of induced field potentials in % of control	IC_{50} µM
Reference compound	10	22	30.0
	20	39	
	40	62	
	80	73	
15 (16)	10	30	21.5
	20	47	
	40	69	
	80	82	

The non-NMDA (quisqualate) antagonist effect was tested in rat neocortex slices by using the method of Harrison and Simmonds [Br. J. Pharmacol. 84, 381 (1981)]. In rat neocortex slices the DC-potential changes induced by quisqualate perfusion were dose-dependently inhibited by the reference compound in the concentration range of 10-50 µM. At the concentration defined, the compound of Example 15 (16) proved to be twice as active as the reference compound in inhibiting the response to the 2-minute perfusion with 10 µM of quisqualate. However, both molecules failed to affect the responses induced by NMDA. Accordingly, the compound of Example 15 (16) can be considered to be a selective, non-NMDA but quisqualate-type excitatory amino acid antagonist.

Acute toxicity in rats

Acute toxicity data obtained in rats are summarized in Table 8.

Table 8

Acute toxicity in rats			
Compound Example No.	Sex	Route of administration	LD_{50} mg/kg
15 (16)	Male	i.p.	145 (128-163.1)
	Male	p.o.	≈200
	Female	i.p.	140 (122-161)
	Female	p.o.	235 (190-291)
42	Male	i.p.	155 (109.9-218.5)
	Male	p.o.	>600
	Female	i.p.	180 (156.5-207.0)
	Female	p.o.	>600

At toxic dose levels the compounds induced a dose-dependent muscle tone reduction, ataxia, adynamia, and loss of the righting reflex. The cause of mortality was respiratory insufficiency developing within 1 to 2 hours after i.p. administration and within 10 to 20 hours after oral application.

Based on the above pharmacological results, the compounds of general formula (I) according to the invention possess significant anticonvulsive, muscle-relaxant and excitatory amino acid-antagonist (neuroprotective) effects. Thus, they are therapeutically useful for the treatment of epilepsy as well as various diseases connected with spasms of the skeletal musculature and cerebral ischaemia (stroke).

The invention also relates to pharmaceutical compositions containing compounds of general formula (I) or pharmaceutically acceptable acid-addition salts thereof as active ingredients as well as to the preparation of these compositions.

For therapeutical use, the active compounds according to the invention are suitably formulated to pharmaceutical compositions by admixing them with commonly used nontoxic, inert, solid or liquid pharmaceutical carriers and/or auxiliary materials useful for enteral or parenteral administration. As carriers, e.g. water, gelatine, lactose, starch, pectin, magnesium stearate, stearic acid, talc or vegetable oils can be used. As auxuliary materials, e.g. preservatives and wetting as well as emulsifying, dispersing and aromatizing agents and buffers can be employed.

By using the above-mentioned carriers and auxiliary materials, the active agents of the invention may be transformed to the usual pharmaceutical compositions, e.g. to solid compositions (such as tablets, capsules, pills or suppositories) or liquid compositions (such as aqueous or oily sulutions, suspensions, emulsions or syrups) as well as to injectable solutions, suspensions or emulsions.

For therapeutical purposes, the daily dose of the compounds of the invention amounts commonly to 0.2-1.5 mg/kg of body weight which is administered daily, optionally divided to several doses.

Based on the above facts, the present invention also provides:

- a method of blocking one or more excitatory amino acid receptors in mammals. This method comprises administering to a mammal in need of such treatment a pharmaceutically effective amount of the general formula (I);
- a method of treating epilepsy in mammals. This method comprises administering to the mammal in need of such treatment an antiepileptic amount of a compound of the general formula (I);
- a method of treating spasms of the skeletal musculature in mammals. This method comprises administering to the mammal in need of such treatment a muscle-relaxing amount of a compound of the general formula (I);
- a method of treating cerebral ischaemia (stroke) in mammals. This method comprises administering to the mammal in need of such treatment a pharmaceutically effective amount of a compound of the general formula (I).

The compounds prepared by the process of the invention were identified by elementary analysis, their purity and structure were controlled and confirmed by thin-layer chromatography, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry.

The invention is illustrated in detail by the following non-limiting Examples.

Exampl 1

1-(4-Diacetylaminophenyl)-3-acetyl-4-methylene-7,8-methylenedioxy-4,5-dihydro-3H-2,3-benzodiazepine

2.93 g (0.01 mol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were refluxed with 20 ml of acetic anhydride for 6 hours. The solution was evaporated at reduced pressure, the residue was taken up in 2x20 ml of anhydrous ethanol, the solution was repeatedly evaporated and the resulting residue of 4.55 g was submitted to column chromatography (adsorbent: Kieselgel 60, eluant: ethyl acetate - benzene 4:1). The raw product was triturated with 20 ml of hot isopropanol to yield 1.44 g (34.4 %) of the aimed product, m.p. 240-245 °C (slight decomp.).
$C_{23}H_{21}N_3O_5$ = 419.445

Example 2

1-(4-Formylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

3.0 g (10.2 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were dissolved in 160 ml of dichloromethane and first 2.75 g (13.3 mmol) of dicyclohexylcarbodiimide, then 0.51 ml (13.3 mmol) of 100 % formic acid were added and the reaction mixture was stirred for 2 hours at room temperature. The precipitated N,N'-dicyclohexylurea was filtered, the filtrate was exracted with 2x30 ml of 10 % aqueous sodium carbonate solution, then with 2x30 ml of distilled water, the organic layer was dried and evaporated at reduced pressure. The residue was dissolved in ethyl acetate, filtered and evaporated under reduced pressure. The resulting raw product was recrystallized from 20 ml of 50 % ethanol to yield 2.93 g (89.3 %) of the aimed product, m.p. 152-154 °C (slight decomp.).
$C_{18}H_{15}N_3O_3$ = 321.342

Examples 3 to 7

The compounds of Examples 3 to 7 were prepared by the process described in Example 2.

Example 3

1-(4-Cyanoacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine

$C_{20}H_{16}N_4O_3$ = 360.380, m.p.: 241-243 °C (decomp.).

Example 4

1-(4-Methoxyacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine

$C_{20}H_{19}N_3O_4$ = 365.396, m.p.: 203-205 °C

Example 5

1-(4-Valerylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

$C_{22}H_{23}N_3O_3$ = 377.450, m.p.: 217-219 °C (decomp.).

Example 6

1-(4-Phenylacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine

$C_{25}H_{21}N_3O_3$ = 411.467, m.p.: 245-247 °C (decomp.).

Example 7

1-(4-Cyclopropanecarb nylaminophenyl)-4-methyl-7,8-methylenedi xy-5H-2,3-benzodiazepine

$C_{21}H_{19}N_3O_3$ = 361.407, m.p.: 260-262 °C (decomp.).

Example 8

1-(4-Acetylaminophenyl)-4-m thyl-7,8-methylen dioxy-5H-2,3-benzodiazepine

10 g (34 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were stirred for 3 hours with 100 ml of acetic anhydride. The crystals formed were filtered, washed with 5x10 ml Of anhydrous ethanol and dried, yielding 9.2 g of raw product, m.p. 252-254 °C (decomp.). This product was treated with 45 ml of hot 99.5 % ethanol. After cooling the crystals were filtered, washed with 3x10 ml of ethanol and dried to give 8.68 g (76.1 %) of the aimed product, m.p.: 256-258 °C (decomp.).
$C_{19}H_{17}N_3O_3$ = 335.369

Example 9

1-(4-Propionylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

$C_{20}H_{19}N_3O_3$ = 349.396, m.p.: 228-230 °C (decomp.).
It was prepared by the process described in Example 8.

Example 10

1-(4-Pivaloylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

1.56 ml (11.2 mmol) of triethylamine and 1.38 ml (11.2 mmol) of pivaloyl chloride were added to a solution of 3 g (10.2 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 160 ml of dichloromethane and the reaction mixture was stirred at 25 °C for one hour. The precipitate formed was filtered, washed with 3x5 ml of dichloromethane, then with 3x20 ml of water and dried to yield 1.59 g of pure product, m.p. 225-227 °C (decomp.). The other portion of the product was isolated from the organic phase. The filtrate was extracted with 3x20 ml of water, then with 3x15 ml of 4 % aqueous sodium hydroxide solution, finally with 2x30 ml of water. The organic layer was subsequently dried and evaporated under reduced pressure. The crystalline residue was combined with the former product of 1.59 g and suspended in 20 ml of hot ethanol. The product was filtered after cooling, washed with 3x3 ml of ethanol and dried to yield 3.38 g (87.8 %) of the pure product, m.p.: 225-227 °C (decomp.).
$C_{22}H_{23}N_3O_3$ = 377.450

Example 11

1-(4-Benzoylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

1.0 ml (15 mmol) of benzoyl chloride and 2.1 ml (15 mmol) of triethylamine were added to a solution of 4 g (13.6 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in dichloromethane and the reaction mixture was stirred at 25 °C for 24 hours. The solution was extracted with 3x30 ml of water, 3x20 ml of a 4 % aqueous sodium hydroxide solution and finally with 2x30 ml of distilled water. The organic layer was dried, evaporated under reduced pressure, then the crystalline residue was treated with 20 ml of hot ethanol to obtain 3.97 g of raw product, m.p. 242-243 °C. This raw product was repeatedly treated with 20 ml of hot ethanol, next day it was filtered at 0-5 °C, washed with 3x3 ml of ethanol and dried at 100 °C to yield 3.85 g (71.3 %) of the pure aimed product, m.p. 246--247 °C (decomp.).
$C_{24}H_{19}N_3O_3$ = 397.40

Example 12

1-(4-Palmitoylaminophenyl)-4-m thyl-7,8-m thylenedioxy-5H-2,3-benzodiazepine

By following the process described in Example 11, with recrystallization of the raw product from 50 % ethanol, the pure aimed product was obtained, m.p. 138-140 °C.
$C_{33}H_{45}N_3O_3$ = 531.747

Example 13

1-(4-Phenylcarbamoylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

0.22 ml (2.04 mmol) of phenyl isocyanate was added to a solution of 0.50 g (1.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 4 ml of dimethylformamide and the reaction mixture was stirred at 25 °C for one hour. Then it was diluted with 20 ml of diethyl ether and filtered at 5 °C. The crystals were washed with 2x5 ml of diethyl ether and dried at 60-100 °C. The resulting 0.70 g of raw product, m.p. 239-240 °C (sintering at 180 °C) was refluxed in 15 ml of ethanol, filtered after cooling, washed wtih 3x1 ml of ethanol and dried at 100 °C to yield 0.55 g (78.6 %) of the aimed product, m.p. 240-241 °C (decomp.).

$C_{24}H_{20}N_4O_3$ = 412.456

Example 14

1-[4-(4-Carboxybutyrylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

A solution of 0.50 g (1.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 30 ml of anhydrous dichloromethane was stirred with 0.18 g (1.87 mmol) of glutaric acid anhydride at 20-25 °C for 6 hours. Next day the crystals formed were filtered at 0-5 °C, washed with 3x2 ml of dichloromethane and dried at 60-80 °C to give 0.60 g (87.0 %) of the pure aimed product, m.p. 225-227 °C (decomp.).

$C_{22}H_{21}N_3O_5$ = 407.434

Example 15

1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

To a solution of 3.58 g (12.1 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 100 ml of chloroform first 1.68 ml (12.1 mmol) of triethylamine, then under constant ice-cooling and stirring 1.15 ml (12.1 mmol) of acetic anhydride were added. Stirring was continued for additional 2 hours, then the solution was extracted with 3x100 ml of water, the organic layer was dried and evaporated under reduced pressure. The crystalline residue was recrystallized from 40 ml of isopropanol to obtain 3.50 g (85.7 %) of the aimed product, m.p. 220-222 °C. After repeated recrystallization the m.p. increased to 223-225 °C.

$C_{19}H_{19}N_3O_3$ = 337.385

Hydrochloride: $(C_{19}H_{20}N_3O_3)Cl$ = 373.850, m.p.: 248-252 °C (decomp.).

Example 16

1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a suspension of 1.91 g (5.37 mmol) of 1-(4-nitrophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (product of Example 27) in 40 ml of methanol about 0.2 g of Raney nickel catalyst and 1.4 ml (28 mmol) of 100 % hydrazine hydrate were added, then the reaction mixture was stirred at 20-25 °C for one hour. The starting nitro derivative was dissolved within 10-20 minutes. After filtering the filtrate was evaporated under reduced pressure, the white crystalline residue was washed with 30 ml of distilled water onto a filter, it was washed with 3x10 ml of distilled water and dried at 100 °C to give 1.50 g of a raw product, m.p. 218-220 °C. This raw product was purified by treating with 12 ml of hot isopropanol. After cooling it was filtered at 5 °C, washed with 3x1 ml of isopropanol and dried at 100 °C to yield 1.40 g (77.35 %) of a white crystalline powder, m.p. 221-223 °C. On the basis of analyses and spectra it was identical to the product of Example 15 obtained by a different process.

Example 17 t 25

The process described in Example 16 was followed for preparing other 1-(4-aminophenyl)-3-R-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepines of the general formula (I). The data of the products prepared are presented in Table 9.

Table 9

Products f the general formula (I) wherein R_2 = CH_3 and R_1 = R_3 = R_4 = H		
Example No.	R	M.p. °C
17	Trifluoroacetyl	215-217
18	Propionyl	211-213
19	Valeryl	178-180
20	Pivaloyl	233-235 (d)
21	Benzoyl	220-222
22	Phenylacetyl	220-221
23	Cyclopropylcarbonyl	138-140
24	Cyanoacetyl	123-126
25	Methoxyacetyl	125-127

(d) = decomposition

The new nitro compounds of the general formula (V), wherein R = H or acyl group, used in the preparation of products of Examples 16 to 25, can be prepared by processes described in Examples 26 to 36.

Example 26

1-(4-Nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a suspension of 5.0 g (15.5 mmol) of the known 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (French patent specification No. 85,09793) in 380 ml of ethanol first 22.5 ml (0.278 mol) of concentrated hydrochloric acid were added at constant stirring whereupon a solution was formed within a few minutes, then 11.5 g (0.3 mole) of sodium borohydride were charged into the solution portionwise during 30 minutes. Stirring was continued for 15 minutes, then the orange-coloured precipitate formed was filtered and extracted on the filter with 4x30 ml of chloroform. The combined chloroform filtrate was evaporated under reduced pressure, the crystalline residue was brought to a filter with 200 ml of distilled water, then washed with 3x20 ml of distilled water and dried at 80-100 °C to yield 4.90 g (97.2 %) of the aimed product, m.p.: 162-164 °C.
$C_{17}H_{15}N_3O_4$ = 325.331

Example 27

1-(4-Nitrophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

A 2.0 g (6.15 mmol) portion of the product of Example 26 was stirred with 10 ml of acetic anhydride at 25 °C for 3 hours then 50 ml of distilled water were added and the stirring was continued for one hour. The yellow precipitate formed was filtered, washed with 3x10 ml of distilled water and dried at 80-100 °C to obtain 2.6 g of raw product. After recrystallization from 10 ml of ethanol 1.94 g (85.8 %) of the aimed product were obtained, m.p.: 140-142 °C.
$C_{19}H_{17}N_3O_5$ = 367.369

Example 28

1-(4-Nitrophenyl)-3-trifluoroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a solution of a 1.5 g (4.61 mmol) portion of the product of Example 26 in 30 ml of anhydrous dichloromethane 0.75 ml (5.3 mmol) of trifluoroacetic acid anhydride and 0.75 ml (5.3 mmol) of triethylamine were added and the reaction mixture was stirred at 25 °C for 3 hours. Subsequently, the mixture was extracted with 3x20 ml of water and the organic layer was dried and evaporated under reduced pressure. The crystalline residue was treated with 15 ml of hot ethanol, cooled, filtered, washed with 3x1 ml of ethanol and dried at 80-100 °C to yield 1.84 g (94.85 %) of the aimed compound as a bright yellow crystalline product, m.p.: 165-167 °C (decomp.).

$C_{19}H_{14}F_3N_3O_5$ = 421.339

Example 29

1-(4-Nitrophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

A 1.54 g (4.7 mmol) portion of the product of Example 26 was stirred with 8 ml of propionic acid anhydride at 25 °C for 3 hours, then 30 ml of diethyl ether were added and the solution was kept at 0-5 °C overnight. The precipitate formed was filtered, washed with 3x8 ml of diethyl ether and dried to yield 1.32 g (73.7 %) of the aimed compound as a light yellow product, m.p.: 189-190 °C.
$C_{20}H_{19}N_3O_5$ = 381.396

Example 30

1-(4-Nitrophenyl)-3-valeryl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a solution of a 2.5 g (7.68 mmol) portion of the product of Example 26 in 40 ml of anhydrous dichloromethane 4.75 g (23 mmol) of dicyclohexylcarbodiimide and 2.88 g (23 mmol) of n-valeric acid were added and the reaction mixture was maintained at 25 °C under intermittent stirring for 24 hours. Then the N,N'-dicyclohexylurea formed as by-product was filtered, the filtrate was evaporated under reduced pressure, the residue was mixed with 2x40 ml of distilled water, decanted and the wet product was left to solidify under 50 ml of 50 % ethanol. The solid compound was filtered, washed with 2x10 ml of 50 % ethanol and dried at 80 °C. The raw product obtained was recrystallized from 24 ml of ethanol and the crystals were dried at 100 °C to yield 2.20 g (70 %) of the aimed product as a yellow powder, m.p.: 145-147 °C.
$C_{22}H_{23}N_3O_5$ = 409.450

Example 31

1-(4-Nitrophenyl)-3-pivaloyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 28 but applying pivaloyl chloride insted of trifluoroacetic acid anhydride, 1.68 g (89.4 %) of the aimed product were obtained, m.p.: 164-166 °C.
$C_{22}H_{23}N_3O_5$ = 409.450

Example 32

1-(4-Nitrophenyl)-3-benzoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 31 but using benzoyl chloride as acyl chloride, 1.72 g (86.9 %) of an ochre yellow product were obtained, m.p.: 222-224 °C (decomp.).
$C_{24}H_{19}N_3O_5$ = 429.440

Example 33

1-(4-Nitrophenyl)-3-phenylacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 30 but using 50 % of the calculated molar amount of dicyclohexylcarbodiimide and phenylacetic acid, a bright yellow product was obtained, m.p.: 193-195 °C.
$C_{25}H_{21}N_3O_5$ = 443.467

Examples 34 to 36

The products of Examples 34 to 36 were obtained by following the process described in Examle 33 and using the respective acid components.

Example 34

1-(4-Nitrophenyl)-3-cyclopr panecarbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

M.p.: 225-228 °C (decomp.).
$C_{21}H_{19}N_3O_5$ = 393.407

Example 35

1-(4-Nitrophenyl)-3-cyanoacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

M.p.: 185-188 °C
$C_{20}H_{16}N_4O_5$ = 392.380

Example 36

1-(4-Nitrophenyl)-3-methoxyacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

M.p.: 187-189 °C
$C_{20}H_{19}N_3O_6$ = 397.396

Example 37

1-(4-Nitrophenyl)-3-(4-carboxybutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By using the product of Example 26 as starting material and performing the acylation according to Example 14 with glutaric acid anhydride, finally recrystallizing the raw product from ethanol the pure aimed product was obtained, m.p.: 148-150 °C.
$C_{22}H_{21}N_3O_7$ = 439.434

Example 38

1-(4-Aminophenyl)-3-phenylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a solution of 0.70 g (2.3 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 10 ml of anhydrous benzene 0.24 ml (2.3 mmol) of phenyl isocyanate was added and the reaction mixture was refluxed for one hour. Thereafter the solution was evaporated under reduced pressure and the amorphous residue was mixed with 20 ml of hot 50 % ethanol. The suspension was cooled to 0 °C and filtered to yield 0.76 g of a raw product, m.p. 190-200 °C. After recrystallization from 99.5% ethanol and trituration with ethyl acetate the aimed compound melts at 207-209 °C.
$C_{24}H_{22}N_4O_3$ = 414.472

The preparation of the starting material of this example was described in the Hungarian patent specification No. 198,494. However, the compound may also be prepared by a new method according to the process of Example 16, by using the compound of Example 26 as starting material to give excellent yields (84 %). The raw product may be recrystallized from 50 % ethanol, m.p.: 118-120 °C.

Example 39

1-(4-Diacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

2.0 g (6.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were refluxed with 40 ml of acetic anhydride for 3 hours, then it was evaporated to dryness under reduced pressure. The crystalline residue was transferred with 25 ml of water to a filter and washed with 5x3 ml of water. After drying 2.79 g of the raw triacetyl derivative were obtained. After washing with 20 ml of isopropanol and drying at 100 °C 2.39 g (84.6 %) of the pure aimed product were obtained, m.p. 224-227 °C.
$C_{23}H_{23}N_3O_5$ = 421.461

Example 40

N^1-[4-(3-Ac tyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N^3-methylurea

0.70 g (2 mmol) of the product of Example 15 was dissolved in benzene dehydrated over calcium hydride, 0.3 ml (5 mmol) of methyl isocyanate was added and the reaction mixture was stirred at 50 °C for 4 hours. The crystals formed after coling were filtered, washed with 3x3 ml of benzene, then triturated with 20 ml of hot benzene. The hot mixture was filtered, the precipitate was washed with 3x3 ml of benzene and dried to give 0.65 g (79.6 %) of the aimed product, m.p.: 168-170 °C (decomp.).
$C_{21}H_{22}N_4O_4$ = 394.439

Example 41

N^1-[4-(3-Acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N^3-phenylurea

By following the process described in Example 40 but using phenyl isocyanate instead of methyl isocyanate, refluxing the reaction mixture for 10 hours, evaporating it under reduced pressure, then suspending the residue first in 50 ml of diethyl ether and then in 15 ml of ethyl acetate, 0.69 g (75.7 %) of the aimed product was obtained, m.p.: 184-186 °C (decomp.).
$C_{26}H_{24}N_4O_4$ = 456.510

Example 42

1-(4-Acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.3 g (4.4 mmol) of 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were stirred at 20-25 °C with 5 ml of acetic anhydride for one hour, then the yellow solution was poured into 100 g of ice-water and stirred until the decomposition of the excess anhydride became complete. The precipitate formed was filtered, washed with 3x10 ml of distilled water and dried to give 1.6 g of raw product. After recrystallization from 20 ml of benzene 1.50 g (89.85 %) of the aimed product were obtained, m.p.: 158-160 °C (decomp.).
$C_{21}H_{21}N_3O_4$ = 379.423

Example 43

1-(4-Formylaminophenyl)-3-formyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To 6.0 ml (0.104 mol) of acetic anhydride 3.0 ml (0.08 mol) of 100 % formic acid were added dropwise at 0 °C during 5 minutes while constant stirring. The stirring was continued at 50 °C for 15 minutes. Thereafter 1 g (3.3 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3--benzodiazepine was added to the thus-prepared mixed anhydride. The reaction mixture was stirred at 25 °C for 1.5 hours, then poured into ice-water, the precipitate formed was filtered, washed with 4x5 ml of distilled water and dried at 80 °C to give 0.80 g of raw product. After crystallization from 3 ml of ethyl acetate 0.65 g (56.2 %) of the aimed product was obtained, m.p.: 193-195 °C.
$C_{19}H_{17}N_3O_4$ = 351.369

Example 44

1-(4-Trifluoroacetylaminophenyl)-3-trifluoroacetyl-4-methyl-7,8-methxlenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.48 g (5 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were dissolved in 30 ml of anhydrous chloroform, then 2.1 ml (15 mmol) of triethylamine and at 20-25 °C 2.12 ml (15 mmol) of trifluoroacetic anhydride were added and the reaction mixture was stirred for 2.5 hours, then extracted first with 2x30 ml of water and thereafter with 20 ml of 5 % hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate, evaporated under reduced pressure and the

amorphous residue was recrystallized from 10 ml of 70 % ethanol to give 1.41 g (57.9 %) of the aimed diacyl derivative, m.p. 177-178 °C.
$C_{21}H_{15}F_6N_3O_4$ = 487.363

Example 45

1-(4-Propionylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

The process described in Example 44 was followed, except that 11.2 mmol of both triethylamine and propionic acid anhydride were used and the crystalline residue was recrystallized first from 15 ml of 50 % ethanol, then from 11.5 ml of 99 % ethanol to give 2.48 g (60.9 %) of the aimed product, m.p.: 152-154 °C.
$C_{23}H_{25}N_3O_4$ = 407.477

Examples 46 to 65

Other diacyl derivatives of the general formula (I), wherein R = acyl group, R^1 = R^3 = H, R^2 = CH_3 and R^4 = acyl group, where R and R^4 are the same or different, are presented in Table 10. These compounds were prepared partly from compounds of the general formula (III), wherein R = R^1 = = R^3 = H and R^4 = acyl group; and partly from new compounds of the general formula (I), wherein R = acyl group, R^1 = R^3 = = R^4 = H and R^2 = CH_3, according to processes defined in the preceding examples.

The preparation of starting substances of general formula (III), wherein R = R^1 = R^3 = H and R^4 = acyl group is illustrated in detail below on the derivative bearing acetyl group as R^4:

1-(4-Acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

Method A)

To a solution containing 6.0 g (20 mmol) 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 30 ml of ethyl acetate 1.38 ml (21 mmol) of methanesulfonic acid were added. The crystalline precipitate was filtered and washed with 5 x 5 ml of ethyl acetate. The dry weight of the product was 7.37 g, m.p.: it sintered above 190 °C and weakly decomposed at 210-212 °C. The thus-obtained methanesulfonate salt of the starting substance was acetylated as follows:

7.37 g of the powdered salt were suspended in 110 ml of acetic anhydride, the suspension was stirred at room temperature for 2 hours, then the crystalline precipitate was filtered, washed with 5 x 10 ml of ethyl acetate and dried to give 6.54 g of methanesulfonate salt of the target compound, m.p. 240-241 °C (with decomposition).

The base was liberated from the methanesulfonate salt of the target compound e.g. in the following way: 6.54 g of salt were dissolved in 90 ml of water, the solution was clarified by charcoal, then 3.6 g of sodium hydrogen carbonate were portionwise added to the clear solution. The precipitate was filtered, washed with 5 x 10 ml of water and dried to obtain 5.54 g of crude product. After recrystallization from 130 ml of isopropanol, 3.11 g (yield 46 %) of product were obtained, m.p.: 221-223 °C (weak decomposition), the melting point of which increased to 223-225 °C after digesting with 15 ml of hot benzene.
$C_{19}H_{19}N_3O_3$ = 337.385

The hydrochloride salt decomposed at 262-264 °C.

Method B)

After dissolving 15.0 g (44.7 mmol) of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 150 ml of pyridine under mild heating, 10.2 g (0.269 mol) of sodium borohydride were added and the mixture was stirred on an oil bath at a temperature of 100 °C for 5 hours. Then the reaction mixture was cooled to about 25 °C, 150 ml of water were dropwise added under continuous stirring during 20 minutes, thereafter a mixture containing 180 ml of concentrated hydrochloric acid and 265 ml of water was added while cooling with ice-water. A yellowish suspension was formed. The precipitate was filtered, washed with 5 x 20 ml of water and dried to yield 15.2 g of salt, m.p. above 250 °C. In order to liberate the base, this salt was suspended in 150 ml of 50 % ethanol and then 5.7 g of sodium hydrogen carbonate were portionwise added while stirring. The thus-formed suspension was filtered after 30 minutes, washed successively with 3 x 10 ml of 50 % ethanol, 5 x 20 ml of water, finally with 20 ml of 50 % ethanol and

dried to obtain 10.95 g of a crude product, m.p.: 218-220 °C (weak decomposition). After digesting this crude product with 50 ml of hot isopropanol and then with 100 ml of hot 99.5 % ethanol, 8.63 g (57.2 %) of the aimed compound were obtained, m.p.: 220-222 °C (weak decomposition).

Physical characteristics of other 1-(4-acylamino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3 -benzodiazepine are as follows:

R^4-Analogue	M.p. °C
Propionyl	237-239
Benzoyl	247-248 (decomp.)
Phenylacetyl	213-215 (decomp.)
Pivaloyl	132-135 (decomp.)

Table 10

Compounds of the general formula (I), wherein $R^1 = R^3 = H$, $R^2 = CH_3$, R and R^4 are acyl groups

Example No.	R	R^4	Starting material Example No.	Process of Example No.	M.p. °C
46	$COCH_3$	CHO	15 (16)	2, 30	142-144
47	$COCF_3$	$COCH_3$	(III), $R^4 = COCH_3$	28, 44	212-214
48	$COCH_3$	COC_2H_5	15 (16)	28, 44	155-157
49	COC_2H_5	$COCH_3$	(III), $R^4 = COCH_3$	28, 44	168-170
50	$COCH_3$	$CO\text{-}C(CH_3)_3$	15 (16)	31	201-203
51	$CO\text{-}C(CH_3)_3$	$COCH_3$	(III), $R^4 = COCH_3$	31	138-140
52	$COCH_3$	$CO\text{-}CH_2\text{-}OCH_3$	15 (16)	2, 30	118-120
53	$CO\text{-}CH_2\text{-}OCH_3$	$COCH_3$	(III), $R^4 = COCH_3$	2, 30	136-138 (d)
54	$COCH_3$	$CO\text{-}CH_2\text{-}CN$	15 (16)	2, 30	149-151 (d)
55	$CO\text{-}CH_2\text{-}CN$	$COCH_3$	(III), $R^4 = COCH_3$	2, 30	128-130 (d)
56	$CO\text{-}C_6H_5$	$COCH_3$	(III), $R^4 = COCH_3$	31	154-156
57	$COCH_3$	$CO\text{-}C_6H_5$	15 (16)	31	214-216

Table 10 (contd.)

Example No.	R	R^4	Starting material Example No.	Process of Example No.	M.p. °C
58	$CO-(CH_2)_3-COOH$	$COCH_3$	(III), R^4 = $COCH_3$	14	172-174
59	$COCH_3$	$CO-(CH_2)_3-COOH$	15 (16)	14	210-212 (d)
60	CHO	COC_2H_5	(III), R^4 = COC_2H_5	2	185-187
61	CHO	$CO-C(CH_3)_3$	(III), R^4 = $CO-C(CH_3)_3$	2	220-221 (d)
62	$COCH_3$	$COCF_3$	15 (16)	28	150-152 (d)
63	CHO	$CO-C_6H_5$	(III), R^4 = $CO-C_6H_5$	2	202-203 (d)
64	$COCH_3$	$CO-CH_2-C_6H_5$	(III), R^4 = $CO-CH_2-C_6H_5$	2	135-137
65	COC_2H_5	CHO	18	2	140-141 (d)

(d) = decomposition

Example 66

1-(4-Glycylaminophenyl)-4-methyl-7,8-m thylenedi xy-5H-2,3-benzodiazepine

To a suspension of 2.89 g (5.97 mmol) of 1-(4-phthaloylglycylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (Example 79) in 50 ml of methanol 0.6 ml (11.9 mmol) of 100 % hydrazine hydrate was added and the mixture was refluxed for 2 hours. The reaction mixture was cooled, evaporated under reduced pressure, the partially crystalline residue was mixed with 40 ml of dichloromethane, filtered and the by-product was washed with 2x10 ml of dichloromethane. The solution was extracted with 3x15 ml of 5 % hydrochloric acid, the aqueous layer was made alkaline with 24 ml of aqueous 10 % sodium hydroxide, the precipitate formed was filtered, washed with 3x10 ml of distilled water and dried at 100 °C to obtain 1.67 g of raw product. After recrystallization from 73 ml of ethanol 1.50 g (71.8 %) of the aimed product were obtained, m.p.: 223-225 °C.

$C_{19}H_{18}N_4O_3$ = 350.385

Examples 67 to 78

Other compounds of the general formula (I), wherein R^2 = CH_3, R^3 = H, and some of their acid addition salts, prepared by the process of Example 66, are presented in Table 11. The salts were prepared by known methods.

Table 11

Example No.	R	R^1	R^4	Example No. of starting material	M.p. °C (salt)
67	-	-	$CO-(CH_2)_3-NH_2$	80	198-200 (d)
68	-	-	$DL-CO-CH(CH_3)-NH_2$	81	155-157 (d)
69	-	-	$DL-CO-CH(CH_3)-NH_2$	68	217-219 (d) (H-Fu)
70	$CO-CH_2-NH_2$	H	H	82	150-155
71	$CO-CH_2-NH_2$	H	H	70	190-193 (d) (H-Fu)
72	$DL\ -CO-CH(CH_3)-NH_2$	H	H	84	193-195 (H-Fu 210-213 (d)]
73	$COCH_3$	H	$CO-CH_2-NH_2$	88	210-211 (d) (HCl) [base 230-232 (d)]
74	$CO-CH_2-NH_2$	H	$COCH_3$	89	210-212 (d)
75	$CO-(CH_2)_3-NH_2$	H	$COCH_3$	90	154-156 (d) (Fu)
76	(H-Fu), $COCH_3$	H	$DL-CO-CH(CH_3)-NH_2$	91	222-223 (d) (H-Fu)
77	$DL\ -CO-CH(CH_3)-NH_2$	H	$COCH_3$	92	218-220 (d)
78	$CO-CH_2-NH_2$	H	$CO-CH_2-NH_2$	93	202-204 (d)

Notes: H-Fu = hydrogen fumarate (H-fumarate), Fu = fumarate
The products of Examples 70 to 72 were prepared from the corresponding starting substances in two steps, by following first Example 66 and then Example 16.

Example 79

1-[4-(N-Phthaloylglycylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

To a solution of 2.0 g (6.88 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in dichloromethane 1.84 g (8.94 mmol) of dicyclohexylcarbodiimide and 1.84 g (8.94 mmol) of powdered phthalimidoacetic acid were added and the reaction mixture was stirred at 25 °C for 8 hours, then left to stand at 0-5 °C overnight. The precipitate formed was filtered, washed with 3x3 ml of dichloromethane and dried at 60-80 °C to result in 5 g of a product consisting of a mixture of the target product and N,N'-dicyclohexylurea, a by-product. This mixture was purified by refluxing with 210 ml of ethanol for 30 minutes, filtering the hot mixture and washing with 2x10 ml of hot ethanol, thereafter drying at 100 °C to obtain 2.42 g (73.3 %) of the aimed product, m.p.: 266-268 °C (decomp.).
$C_{27}H_{20}N_4O_5$ = 480.489

Example 80

1-[4-(N-Phthaloyl-γ-aminobutyrylamino)phenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

By following the process described in Example 79 but using γ-phthalimidobutyric acid, 3.8 g of a mixture were obtained, which was combined with the dichloromethane mother liquor extracted previously with 2x40 ml of a 10 % aqueous sodium carbonate solution. After evaporating under reduced pressure the residue was submitted to column chromatography [adsorbent: Kieselgel 60 (0.063-2 mm), eluent: ethyl acetatemethanol 4:1]. The evaporation residue was triturated with 10 ml of hot ethanol, cooled, filtered, washed with 3x1 ml of ethanol and dried to give 3.12 g (90 %) of the aimed product, m.p.: 233-235 °C (decomp.).
$C_{29}H_{24}N_4O_5$ = 508.543

Example 81

1-[4-(N-Phthaloyl-DL-alanylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

The process described in Example 79 was followed, except that N-phthaloyl-DL-alanine (DL-2-phthalimido-propionic acid) was used. After filtering the slight precipitate formed the filtrate was evaporated, the residue was mixed with 15 ml of dichloromethane, carefully filtered and the clear solution obtained was repeatedly evaporated. The purification of the residue was achieved by refluxing it with 60 ml of ethyl acetate. Crystal formation was already started in the hot solution. The crystals were filtered at 0-5 °C, the nearly white crystal powder was washed with 3x3 ml of ethyl acetate and dried at 100 °C to give 2.75 g (80.95 %) of the aimed product, m.p.: 243-245 °C (decomp.).
$C_{28}H_{22}N_4O_5$ = 494.516

Example 82

1-(4-Nitrophenyl)-3-glycyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

The process described in Example 66 was followed by using the compound prepared according to Example 85 as starting material, but the dichloromethane solution was extracted only with 3x20 ml of distilled water and the organic layer was evaporated under reduced pressure. The crystalline residue was purified by suspending it in 7 ml of ethanol to give the pure aimed product in a yield of 86.1 %, m.p.: 201-203 °C (decomp.).
$C_{19}H_{18}N_4O_5$ = 382.385

Example 83

1-(4-Nitrophenyl)-3-(γ-aminobutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 82 and using the compound prepared according to Example 86 as starting material, a product containing crystal solvent was obtained in a yield of 89.4 %, m.p. 110-112 °C (recrystallized from 50 % ethanol).
$C_{21}H_{22}N_4O_5$ = 410.439

Example 84

1-(4-Nitrophenyl)-3-(DL-alanyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 82 and using the compound pepared according to Example 87 the aimed compound was obtained, m.p. 220-221 °C (decomp.).
$C_{20}H_{20}N_4O_5$ = 396.412

Examples 85 to 87

The new intermediates employed in Examples 82 to 84 as starting materials were prepared from the compound prepared according to Example 26 by the process of Example 81.

Example 85

1-(4-Nitrophenyl)-3-(N-phthaloylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

Yield: 93.3 %, m.p.: 173-174 °C (decomp.).
$C_{27}H_{20}N_4O_7$ = 512.489

Example 86

1-(4-Nitrophenyl)-3-(N-phthaloyl-γ-aminobutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

M.p.: 218-220 °C
$C_{29}H_{24}N_4O_7$ = 540.543

Example 87

1-(4-Nitrophenyl)-3-(N-phthaloyl-DL-alanyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

M.p.: 210-212 °C
$C_{28}H_{22}N_4O_7$ = 526.516

Example 88 to 94

The intermediates of the general formula (I), wherein R and/or R4 represent(s) C_{1-6} acyl group(s) substituted by a phthalimido group, are required for the preparation of compounds obtained by using the processes of Examples 73 to 78 and summarized in Table 12. They were prepared from the compound of Example 15 (16) or from a compound of the general formula (III), wherein R_4 is hydrogen (see U.S. patent specification No. 4,835,152) or from 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine described hereinabove (before Table 10) by following the process of Example 81.

As a matter of course, in Example 93 a twofold amount of phthaloylglycine and dicyclohexylcarbodiimide have to be used. Thus, Table 12 lists new compounds of the general formula (I), wherein R and R^4 are acyl groups, R^1 = R^3 = H and R^2 = CH_3.

Table 12

Example No.	R	R^4	M.p. °C
88	$COCH_3$	$CO-CH_2-N(CO)_2C_6H_4$	314-316 (d)
89	$CO-CH_2-N(CO)_2C_6H_4$	$COCH_3$	204-206 (d)
90	$CO-(CH_2)_3-N(CO)_2C_6H_4$	$COCH_3$	150-152
91	$COCH_3$	DL $-CO-CH(CH_3)-N(CO)_2C_6H_4$	264-266 (d)
92	DL $-CO-CH(CH_3)-N(CO)_2C_6H_4$	$COCH_3$	245-248
93	$CO-CH_2-N(CO)_2C_6H_4$	$CO-CH_2-N(CO)_2C_6H_4$	230-232 (d)
94	$COCH_3$	$CO-(CH_2)_3-N(CO)_2C_6H_4$	173-175

$(CO)_2C_6H_4$ = phthaloyl; $N(CO)_2C_6H_4$ = phtalimido; (d) = decomposition

Example 95

1-(4-Aminophenyl)-3-(γ-aminobutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrogen fumarate

It was prepared from the compound of Example 83 by following Example 16, m.p.: 150-152 °C (decomp.)

$[C_{29}H_{25}N_4O_3]^*C_4H_3O_4$ = 496.531

Example 96

1-(4-Aminophenyl)-3-(4-carboxybutyryl)-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrochloride

It was obtained from the compound of Exyample 37, according to Example 16, m.p.: 224-226 °C (decomp.).
$[C_{22}H_{24}N_3O_5]Cl$ = 445.915

Example 97

1-(4-Trifluoroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

It was prepared by following Example 2, m.p.: 258-260 °C (decomp.).
$C_{19}H_{14}F_3N_3O_3$ = 389.339

Example 98

1-(4-Aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-(4-nitrophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine according to Example 16, m.p. 199-201 °C.
$C_{19}H_{20}N_4O_3$ = 352.401
Hydrochloride m.p. 219-221 °C (decomp.).
$[C_{19}H_{21}N_4O_3]Cl$ = 388.866
The starting nitro compound was prepared as follows:
1.1 ml (18.4 mmol) of methyl isocyanate were added to 3.0 g (9.22 mmol) of 1-(4-nitrophenyl)-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 26) dissolved in 60 ml of dichloromethane and stirred for 24 hours, then evaporated under reduced pressure. The crystalline residue was triturated with 30 ml of hot ethanol at 80 to 100 °C to obtain 3.35 g (95 %) of the lemon-yellow aimed product, m.p.: 238-240 °C (decomp.).
$C_{19}H_{18}N_4O_5$ = 382.385

Example 99

1-(4-Aminophenyl)-3-(1-pyrrolidinoacetyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was obtained from 1-(4-nitrophenyl)-3-(1-pyrrolidino-acetyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by following Example 16, m.p.: 212-214 °C.
$C_{23}H_{26}N_4O_3$ = 406.493
The starting substance was obtained from 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 116) according to Example 102, m.p.: 189-190 °C (decomp.).
$C_{23}H_{24}N_4O_5$ = 436.477

Example 100

1-(4-Aminophenyl)-3-(N,N-dimethylglycyl)-4-methyl-7,8-methylen dioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrog n fumarate

It was prepared fr4om 1-(4-nitrophenyl)-3-(N,N-dimethylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodizapine according to Example 16, m.p.: 202-204 °C (decomp.).
$[C_{21}H_{25}N_4O_3]C_4H_3O_4$ = 496.531
The starting substance was obtained from 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-

3,4-dihydro-5H-2,3-benzodiazepine according to the process described in Example 103, m.p.: 158-160 °C.
$C_{21}H_{22}N_4O_5$ = 410.439

Example 101

1-(4-Chloroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

It was prepared according to Example 2, except that chloroacetic acid was used, m.p.: 209-214 °C (carbonization).
$C_{19}H_{16}ClN_3O_3$ = 369.818

Example 102

1-[4-(1-Pyrrolidinoacetylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

0.71 ml (8.53 mmol) of pyrrolidine was added to a suspension of 1.5 g (406 mmol) of 1-(4-chloroacetyl-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 60 ml of ethanol and the reaction mixture was refluxed for 4 hours, then evaporated under reduced pressure. The residue was treated with water to give a rough product (1.49 g), m.p.: 186-188 °C. After recrystallization from 12 ml of ethanol 1.22 g (74.4 %) of the aimed product were obtained, m.p.: 210-212 °C.
$C_{23}H_{24}N_4O_3$ = 404.477

Example 103

1-[4-(N,N-dimethylglycylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

After adding 0.66 g (8.12 mmol) of dimethylamine hydrochloride and 1.86 ml (13.4 mmol) of triethylamine to a suspension of 1.5 g (4.06 mmol) of 1-(4-chloroacetyl-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 60 ml of ethanol, the reaction mixture was refluxed for 8 hours, then evaporated. The residue was dissolved in 30 ml of dichloromethane, washed with 20 ml of 4 % NaOH solution, then 2x20 ml of distilled water, dried and evaporated under reduced pressure. After treating with water, the crystalline residue was filtered to give 1.27 g of raw product, m.p. 211-213 °C. After recrystallization from 10 ml of ethanol 1.1 g (71.4 %) of aimed product were obtained, m.p.: 213-215 °C.
$C_{21}H_{22}N_4O_6$ = 378.439

Example 104

1-(4-Methylcarbamoylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

0.8 ml (13.4 mmol) of methyl isocyanate was added to a solution containing 1.0 g (3.41 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 8 ml of dimethylformamide (DMF), then the reaction mixture was stirred at 25 °C for 24 hours. After diluting with 80 ml of water, filtering at 5 °C and drying at 60 to 100 °C, 1.06 g of raw product, m.p.: 204-207 °C (sintering from 160 °C) were obtained which, when recrystallized from 5 ml of ethanol, gave 0.85 g (71.4 %) of the aimed product, m.p.: 223-224 °C (decomp.).
$C_{19}H_{18}N_4O_3$ = 350.385

Example 105

1-(4-Acetylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 42. The raw product was recrystallized from ethyl acetate to give 71.4 % of the aimed product, m.p.: 150-152 °C.
$C_{21}H_{22}N_4O_4$ = 394.439

Example 106

1-(4-Chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 2, m.p.: 139-140 °C. $C_{21}H_{20}ClN_3O_4$ = 413.972

Example 107

1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from the product of the preceding Example by using the process described in Examle 103, m.p.: 206-208 °C.
$C_{23}H_{26}N_4O_4$ = 422.493

Example 108

1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine and diethylamine by using the process described in Example 102, m.p.: 175-176 °C.
$C_{25}H_{30}N_4O_4$ = 450.547

Example 109

1-[4-(1-Pyrrolidinoacetylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrogen fumarate

It was prepared from 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 2 and isolated in the form of hydrogen fumarate, m.p.: 181-183 °C (decomp.).
$[C_{25}H_{29}N_4O_4]^{\bullet}C_4H_3O_4$ = 564.607

Example 110

1-(4-Acetylaminophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from the compound of general formula (III), wherein R^4 = $COCH_3$, by using the process of Examle 2 and chloroacetic acd instead of formic acid, m.p. 138-140 °C.
$C_{21}H_{20}ClN_3O_4$ = 413.972

Example 111

1-[4-(N,N-diethylglycylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

It was prepared from 1-(4-chloroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine by using the process of Example 102, except that diethylamine was used instead of pyrrolidine, m.p.: 157-158 °C.
$C_{23}H_{26}N_4O_3$ = 406.493

Example 112

1-(4-Acetylaminophenyl)-3-cyclopropanecarbonyl-4-methyl-7,8-methylen dioxy-3,4-dihydro-5H-2,3-benzodiaz pine

It was prepared from 1-(4-aminophenyl)-3-cyclopropane-carbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3--benzodiazepine by using the process of Example 42, m.p.: 242-243 °C.
$C_{23}H_{23}N_3O_4$ = 405.461

Example 113

N^1-[4-(3-Methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N^3-methylurea

After adding 0.5 ml (8.5 mmol) of methyl isocyanate to 0.6 g (1.7 mmol) of 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 98) dissolved in 45 ml of anhydrous dichloromethane, the reaction mixture was stirred at 25 °C for 6 days. Then the crystalline precipitate was filtered, washed with 3x2 ml of dichloromethane and dried at 60 to 80 °C to obtain 0.55 g (79.7 %) of the pure aimed product, m.p.: 181--183 °C.
$C_{21}H_{23}N_5O_4$ = 409.455

Example 114

1-(4-Aminophenyl)-3-n-butylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-(4-nitrophenyl)-3-n-butylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine, m.p.: 173-175 °C.
$C_{22}H_{26}N_4O_3$ = 394.482

The starting substance was prepared as described for the starting substance of Example 98, except that n-butyl isocyanate was used instead of methyl isocyanate and the reaction mixture was stirred for 5 days at 25 °C, m.p. 176-178 °C.
$C_{22}H_{24}N_4O_5$ = 424.466

Example 115

1-(4-Glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-[4-(N-phthaloylglycylamino)-phenyl]-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 66 as modified in Example 82, m.p.: 163-165 °C.
$C_{21}H_{23}N_5O_4$ = 409.455

The starting substance was prepared from 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 98) according to Example 79, m.p. 270-271 °C (decomp.).
$C_{29}H_{25}N_5O_6$ = 539.559

Example 116

1-(4-Aminophenyl)-3-(N-methylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.03 g (15.3 mmol) of methylamine hydrocdhloride and 2.64 ml (18.3 mmol) of triethylamine were added to a suspension containing 1.23 g (3.06 mmol) of 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 140 ml of ethanol and the reaction mixture was refluxed for 10 hours, then evaporated under reduced pressure. The residue was dissolved in 30 ml of chloroform, washed with 20 ml of 4% NaOH solution, then 2x20 ml of water, dried and evaporated under reduced pressure. The residue was reduced according to the process of Example 16 and the product obtained was purified by column chromatography (adsorbent: Kieselgel 60, eluent: methanol - benzene 4:1). The crude product obtained was triturated with 5 ml of ethyl acetate at 25 °C to obtain 0.60 g (53.6 %) of the aimed product, m.p. 198-200 °C (weak decomp.).
$C_{20}H_{22}N_4O_3$ = 366.428)

The starting compound was obtained from 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Examle 26) and chloroacetic acid by using the process of Example 33, m.p. 189-191 °C (decomp.).
$C_{19}H_{16}ClN_3O_5$ = 401.818

Example 117

1-[4-(N-methylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.31 g (19.5 mmol) of methylamine hydrochloride and 3.24 ml (23.3 mmol) of triethylamine were added to a suspension containing 1.61 g (3.89 mmol) of 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 106) in 100 ml of ethanol and the reaction mixture was refluxed for 10 hours, then evaporated under reduced pressure. The residue was purified by column chromatography (adsorbent: Kieselgel 60, eluent: chloroform - methanol 9:1). The crude product was triturated with 3 ml of 50 % ethanol at 25 °C to give 0.61 g (38.6 %) of the aimed product, m.p.: 220-222 °C (weak decomp.).
$C_{22}H_{24}N_4O_4$ = 408.466

Example 118

Preparation of pharmaceutical compositions

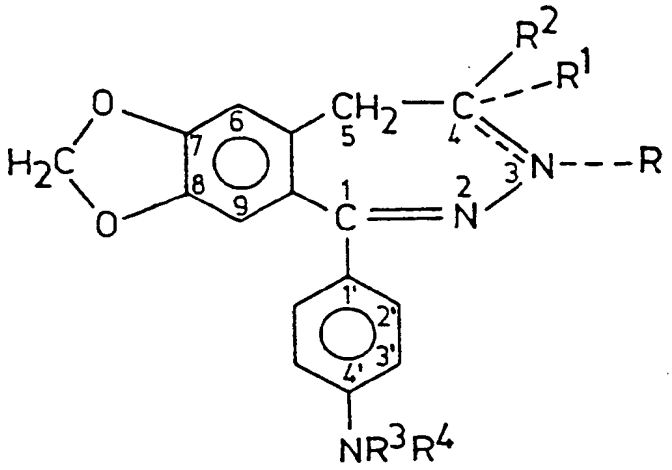
Tablets or divided tablets containing 25 mg of 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Examples 15 or 16) or 25 mg of 1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Example 42) or 25 mg of 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Example 98) each as active ingredient were prepared by usual methods.

a) Composition of one tablet:	
Active ingredient	25 mg
Potato starch	43 mg
Lactose	160 mg
Polyvinylpyrrolidone	6 mg
Magnesium stearate	1 mg
Talc	30 mg

b) An other preferred composition of one tablet:	
Active ingredient	25 mg
Lactose	130 mg
Maize starch	25 mg
Microcrystalline cellulose	10 mg
Gelatine	4 mg
Talc	2 mg
Stearin	1 mg
Magnesium stearate	1 mg

Claims

1. N-Acyl-2,3-benzodiazepine derivatives of the general formula (I)



(I)

wherein

R stands for a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;

R^1 means hydrogen; or R^1 is absent when a double bond exists between the N(3) and C-(4) atoms;

R^2 means a C_{1-3} alkyl group; or

R^1 and R^2 together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;

R^3 means hydrogen or a C_{1-4} aliphatic acyl group;

R^4 represents hydrogen; a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R^3 and R^4 stand for hydrogen,

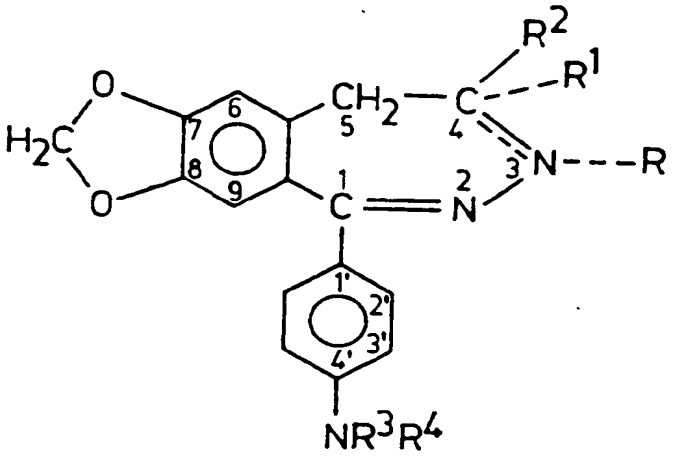
and their stereoisomers as well as acid-addition salts (where possible) of these compounds.

2. A compound selected from the group consisting of 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4 -dihydro-5H-2,3-benzodiazepine,
1-(4-aminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-propionylaminophenyl)-3-propionyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-propionylaminophenyl)-3-acetyl-4-methyl-7,8-methylene -dioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-acetylaminophenyl)-3-propionyl-4-methyl-7,8-methylene -dioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-propionylaminophenyl)-3-formyl-4-methyl-7,8-methylene -dioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-trifluoroacetylaminophenyl)-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-glycylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine hydrochloride,
N^1-[4-(3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H -2,3-benzodiazepine-1-yl)-phenyl]-N^3-methylurea,
1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,

1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-[4-(1-pyrrolidinoacetylamino)phenyl]-3-acetyl-4-methyl -7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine
and hydrogen fumarate thereof and
1-(4-glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine.

3. A pharmaceutical composition, which comprises as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R^1, R^2, R^3, R^4 and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

4. A process for the preparation of the novel N-acyl-2,3-benzodiazepine derivatives of the general formula (I),



(I)

wherein

R stands for a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;

R^1 means hydrogen; or R^1 is absent when a double bond exists between the N(3) and C-(4) atoms;

R^2 means a C_{1-3} alkyl group; or

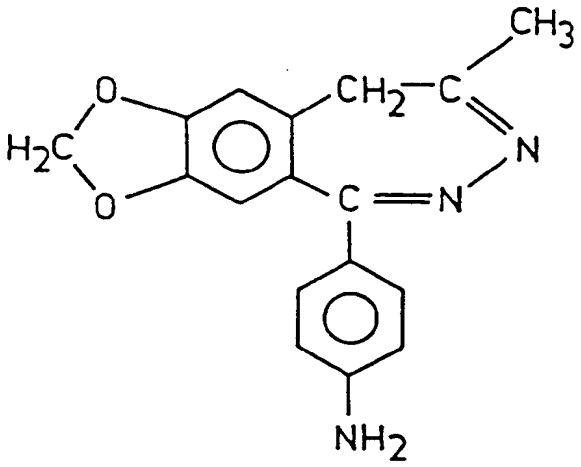
R^1 and R^2 together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;

R^3 means hydrogen or a C_{1-4} aliphatic acyl group;

R^4 represents hydrogen; a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; and

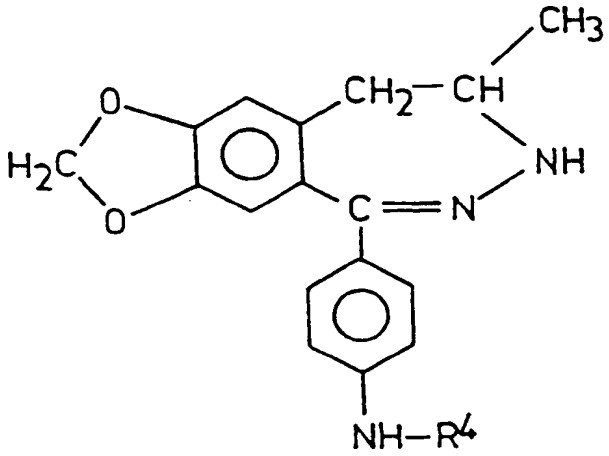
the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R^3 and R^4 stand for hydrogen,
and their stereoisomers as well as acid addition salts, which comprises

a) acylating a compound of formula (II)



(II)

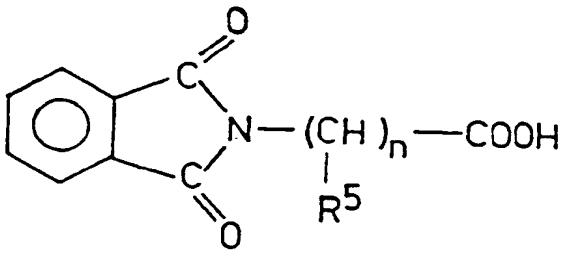
with a C_{1-6} aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R^4 means a C_{1-6} aliphatic acyl group substituted by a halogen, with a C_{1-4} alkylamine, di(C_{1-4} alkyl)amine or pyrrolidine,
to obtain compounds of the general formula (I), wherein R^2, R^3 and the dotted lines are as defined above, R^4 means a C_{1-6} aliphatic acyl group,optionally substituted by a methoxy, cyano, carboxy, phenyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R^1 are absent and a double bond is present between the N(3) and C(4) atoms;
b) acylating a compound of the general formula (III),



(III)

wherein R^4 is as defined above, with a C_{1-6} aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R^4 means a C_{1-6} aliphatic acyl group substituted by a halogen, with a C_{1-4}alkylamine, di(C_{1-4} alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R^1, R^2, R^3, R^4 and the dotted lines are as defined above, R means a C_{1-6} aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino or pyrrolidino group, or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or

c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),



(VI)

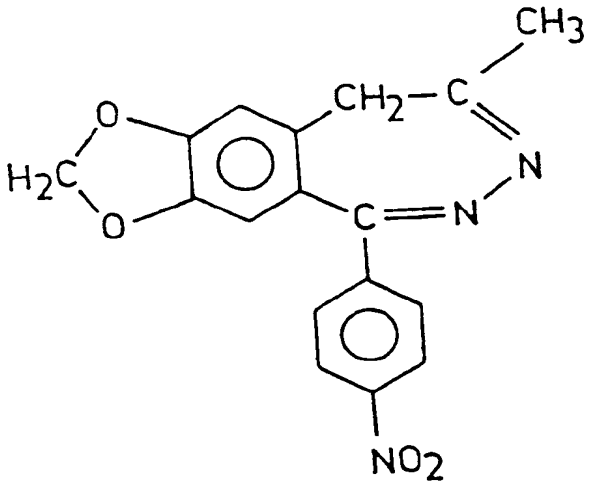
wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 stands for a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group, both R and R^1 are absent, and a double bond is present between the N(3) and C(4) atoms; or

d) acylating a compound of the general formula (III), wherein R^4 is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 is as defined above except hydrogen, R stands for a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

e) reacting a compound of the formula (II) with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 represents a C_{1-5} alkylcarbamoyl or phenylcarbamoyl group, R and R^1 are absent and a double bond is present between the N(3) and C(4) atoms; or

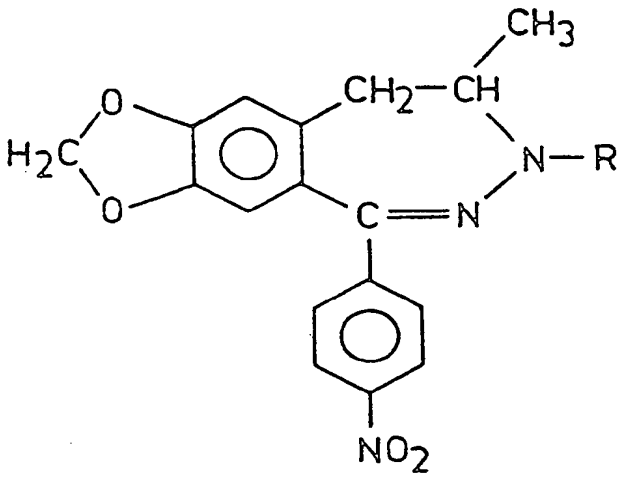
f) reacting a compound of the general formula (III), wherein R^4 is defined as above, with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 is as defined above except hydrogen, R stands for a C_{1-5} alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

g) selectively reducing a nitro compound of the formula (IV)



(IV)

to a novel compound of the general formula (V)



(V)

wherein R means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein R is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein R^4 stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein R^1, R^3 and R^4 represent hydrogen, R^2, R and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

h) acylating a new compound of the general formula (I), wherein R, R^1, R^2 and the dotted lines are as defined above, R^3 and R^4 mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C_{1-6} aliphatic carboxylic acid, optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative thereof, to obtain compounds of the general formula (I), wherein R^1, R^2, R^3 and the dotted lines are as defined above, R and R^4 represent a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N(3) and C(4) atoms; or

i) reacting a new compound of the general formula (I), wherein R, R^1, R^2 and the dotted lines are as delined above, R^3 and R^4 mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R stands for a C_{1-6} aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; R^3 stands for hydrogen; R^4 represents a C_{1-5} alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

j) acylating a new compound of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 and R^4 mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R represents a c_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group; R^3 stands for hydrogen, R^4 represents a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

5. A process as claimed in claim 4, process a) or b), which comprises carrying out the acylation in a suitable solvent, preferably dichloromethane, with a carboxylic acid in the presence of dicyclohexylcarbodiimide at a temperature between 10 °C and 30 °C.

6. A process as claimed in claim 4, process a) or b), which comprises carrying out the acylation in the presence or absence of a solvent by using a carboxylic acid anhydride, mixed anhydride or acyl chloride, optionally in the presence of an acid-binding agent at a temperature between 0 °C and 150 °C.

7. A process as claimed in claim 6, which comprises carrying out the reaction in chloroform or dichloromethane.

8. A process as claimed in claim 4, process e) or f), which comprises carrying out the additive acylation by using a suitable alkyl or phenyl isocyanate in dimethylformamide, benzene or dichloromethane at a temperature between 15 °C and 100 °C.

9. A process as claimed in claim 4, process g), which comprises carrying out the selective reduction of the nitro compound of formula (IV) using sodium borohydride in a C_{1-4} aliphatic alcohol solution.

10. A process as claimed in claim 4, process g) or claim 6, which comprises reducing the nitro group of a compound of the general formula (V) in a methanolic medium by using hydrazine or hydrazine hydrate in the presence of Raney nickel or palladium as catalyst at a temperature between 10 °C and 65 °C.

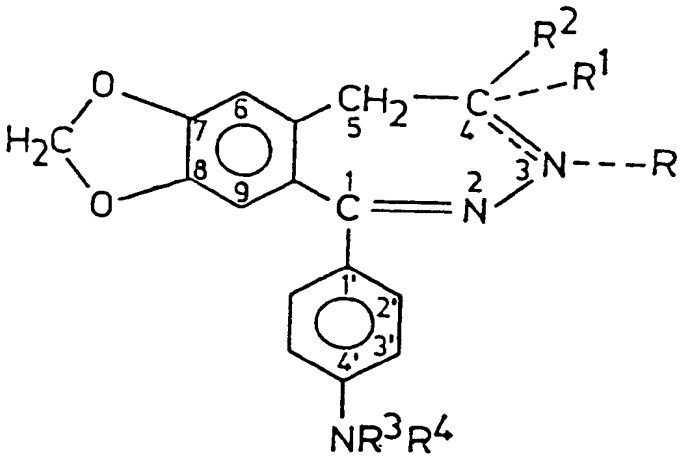
11. A process for the preparation of the pharmaceutical composition according to claim 3, which comprises as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R^1, R^2, R^3, R^4 and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

12. The use of the compounds prepared according to claims 1 to 8 for preparing medicaments, particularly such blocking one or more excitatory amino acid receptors in mammals in need of decreased excitatory amino acid neurotransmission, or such for treating epilepsy in mammals, or such for treating spasms of the skeletal musculature in mammals by muscle-relaxing or for treating cerebral ischaemia (stroke) in mammals.

13. N-Acyl-2,3-benzodiazepine derivatives of the general formula V,
wherein
R means hydrogen or a C_{1-6} aliphatic acyl group; optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group.

Claims for the following Contracting States : GR, ES

1. A process for the preparation of N-acyl-2,3-benzodiazepine derivatives of the general formula (I),



(I)

wherein

R stands for a C_{1-6} aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;

R^1 means hydrogen; or R^1 is absent when a double bond exists between the N(3) and C-(4) atoms;

R^2 means a C_{1-3} alkyl group; or

R^1 and R^2 together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;

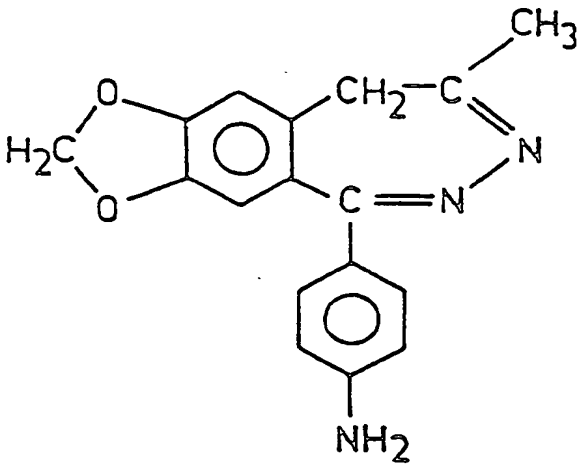
R^3 means hydrogen or a C_{1-4} aliphatic acyl group;

R^4 represents hydrogen; a C_{1-6} aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R^3 and R^4 stand for hydrogen,

and their stereoisomers as well as acid addition salts, which comprises

a) acylating a compound of formula (II)



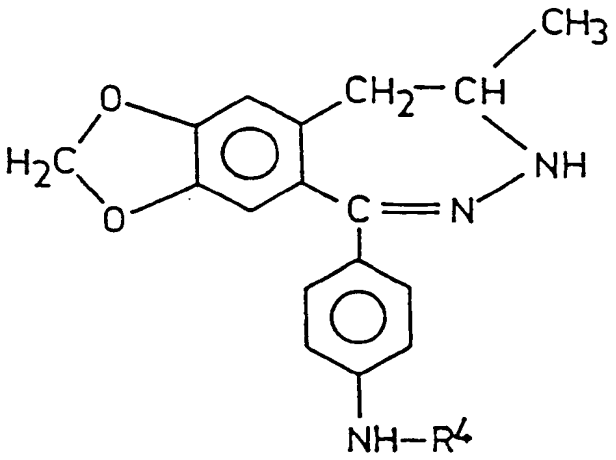
(II)

with a C_{1-6} aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R^4 means a C_{1-6} aliphatic acyl group substituted by a halogen, with a C_{1-4} alkylamine,

di(C_{1-4} alkyl)amine or pyrrolidine,

to obtain compounds of the general formula (I), wherein R^2, R^3 and the dotted lines are as defined above, R^4 means a C_{1-6} aliphatic acyl group,optionally substituted by a methoxy, cyano, carboxy, phenyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R^1 are absent and a double bond is present between the N(3) and C(4) atoms;

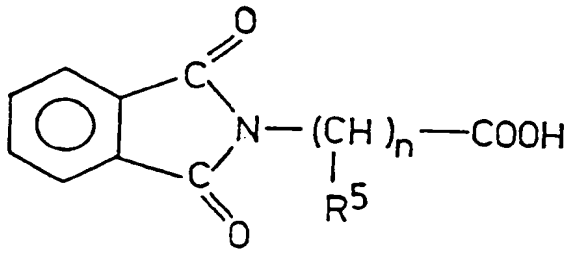
b) acylating a compound of the general formula (III),



(III)

wherein R^4 is as defined above, with a C_{1-6} aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R^4 means a C_{1-6} aliphatic acyl group substituted by a halogen, with a C_{1-4} alkylamine, di(C_{1-4} alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R^1, R^2, R^3, R^4 and the dotted lines are as defined above, R means a C_{1-6} aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino or pyrrolidino group, or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or

c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),



(VI)

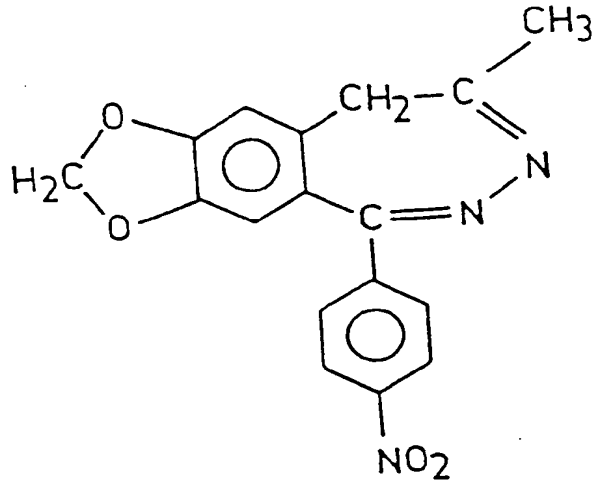
wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 stands for a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group, both R and R^1 are absent, and a double bond is present between the N(3) and C(4) atoms; or

d) acylating a compound of the general formula (III), wherein R^4 is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 is as defined above except hydrogen, R stands for a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

e) reacting a compound of the formula (II) with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 represents a C_{1-5} alkylcarbamoyl or phenylcarbamoyl group, R and R^1 are absent and a double bond is present between the N(3) and C(4) atoms; or

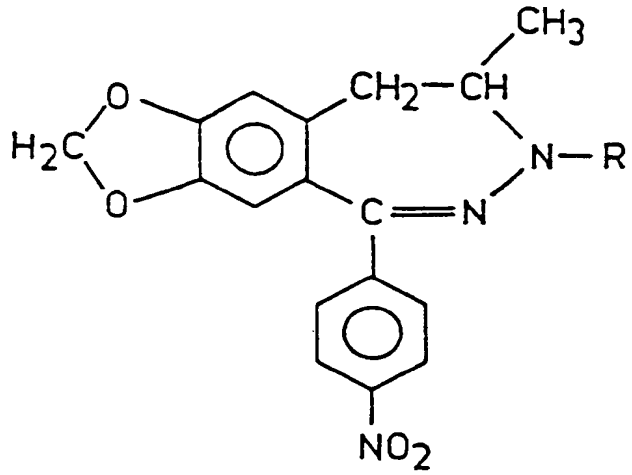
f) reacting a compound of the general formula (III), wherein R^4 is defined as above, with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 means hydrogen, R^4 is as defined above except hydrogen, R stands for a C_{1-5} alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

g) selectively reducing a nitro compound of the formula (IV)



(IV)

to a novel compound of the general formula (V)



(V)

wherein R means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein R is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein R^4 stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein R^1, R^3 and R^4 represent hydrogen, R^2, R and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

h) acylating a new compound of the general formula (I), wherein R, R^1, R^2 and the dotted lines are as defined above, R^3 and R^4 mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C_{1-6} aliphatic carboxylic acid,optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative

thereof, to obtain compounds of the general formula (I), wherein R^1, R^2, R^3 and the dotted lines are as defined above, R and R^4 represent a C_{1-6} aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N(3) and C(4) atoms; or

i) reacting a new compound of the general formula (I), wherein R, R^1, R^2 and the dotted lines are as defined above, R^3 and R^4 mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C_{1-5} alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R stands for a C_{1-6} aliphatic acyl group,optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen-(s); or a benzoyl group; R^3 stands for hydrogen; R^4 represents a C_{1-5} akylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

j) acylating a new compound of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R^3 and R^4 mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein R^5 stands for hydrogen or a C_{1-4} alkyl group and n is 1 in case of α-amino acids, whereas R^5 means hydrogen and n is an integer of 2 to 5 in case of β-ϵ amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R^1, R^2 and the dotted lines are as defined above, R represents a C_{1-6} aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group; R^3 stands for hydrogen, R^4 represents a C_{1-6} aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

2. A process as claimed in claim 1, process a) or b), which comprises carrying out the acylation in a suitable solvent, preferably dichloromethane, with a carboxylic acid in the presence of dicyclohexylcarbodiimide at a temperature between 10 °C and 30 °C.

3. A process as claimed in claim 1, process a) or b), which comprises carrying out the acylation in the presence or absence of a solvent by using a carboxylic acid anhydride, mixed anhydride or acyl chloride, optionally in the presence of an acid-binding agent at a temperature between 0 °C and 150 °C.

4. A process as claimed in claim 3, which comprises carrying out the reaction in chloroform or dichloromethane.

5. A process as claimed in claim 1, process e) or f), which comprises carrying out the additive acylation by using a suitable alkyl or phenyl isocyanate in dimethylformamide, benzene or dichloromethane at a temperature between 15 °C and 100 °C.

6. A process as claimed in claim 1, process g), which comprises carrying out the selective reduction of the nitro compound of formula (IV) using sodium borohydride in a C_{1-4} aliphatic alcohol solution.

7. A process as claimed in claim 1, process g) or claim 3, which comprises reducing the nitro group of a compound of the general formula (V) in a methanolic medium by using hydrazine or hydrazine hydrate in the presence of Raney nickel or palladium as catalyst at a temperature between 10 °C and 65 °C.

8. A process according to anyone of claims 1 to 7, characterized in that a compound selected from the group consisting of

1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4 -dihydro-5H-2,3-benzodiazepine,
1-(4-aminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-propionylaminophenyl)-3-propionyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-propionylaminophenyl)-3-acetyl-4-methyl-7,8-methylene -dioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-acetylaminophenyl)-3-propionyl-4-methyl-7,8-methylene -dioxy-3,4-dihydro-5H-2,3-benzodiazepine,

1-(4-propionylaminophenyl)-3-formyl-4-methyl-7,8-methylene -dioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-trifluoroacetylaminophenyl)-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-glycylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine hydrochloride,
N^1-[4-(3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H -2,3-benzodiazepine-1-yl)-phenyl]-N^3-methylurea,
1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
1-[4-(1-pyrrolidinoacetylamino)phenyl]-3-acetyl-4-methyl -7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine
and hydrogen fumarate thereof and
1-(4-glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine is prepared.

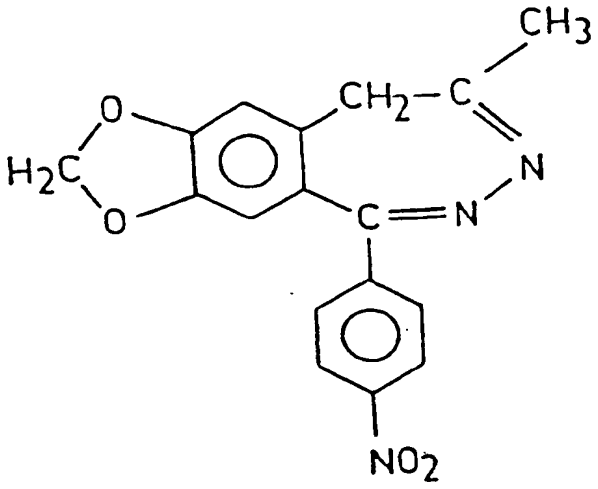
9. A process for the preparation of a pharmaceutical composition which comprises as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R^1, R^2, R^3, R^4 and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry, characterized by admixing as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R^1, R^2, R^3, R^4 and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, prepared by using any of process variants a) to j) as claimed in claim 1, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

10. A process according to claim 9, characterized in that compositions for blocking one or more excitatory amino acid receptors in mammals in need of decreased excitatory amino acid neurotransmission, or for treating epilepsy in mammals, or for treating spasms of the skeletal musculature in mammals by muscle-relaxing or for treating cerebral ischaemia (stroke) in mammals are prepared.

11. A process for preparing N-acyl-2,3-benzodiazepine derivatives of the general formula V, wherein

R means hydrogen or a C_{1-6} aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl group,

characterized by selectively reducing a nitro compound of the formula selectively reducing a nitro compound of the formula (IV)



(IV).

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 12 1882

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	GB-A-2 194 236 (BIOGAL GYOGYSZERGYAR) * page 1, line 40 - line 54; claims 1-5,8-10 * & US-A-4 835 152	1,3,4, 11,12	C07D491/04 A61K31/55 //(C07D491/04, 317:00,243:00)
Y	GB-A-2 162 184 (EGIS GYOGYSZERGYAR) * page 2, line 41 - line 48; claims 1-3,9,10; examples 5,8 * & US-A-4 614 740	1,3,4, 11,12	
Y	CHEMICAL ABSTRACTS, vol. 111, no. 21, 20 November 1989, Columbus, Ohio, US; abstract no. 187314F, I. TARNAWA ET AL.: 'Electrophysiological studies with ...' page 58 ; & Eur. J. Pharmacol. 1989, 167(2), 193-9	1,12	
Y	DE-A-2 353 187 (KALI-CHEMIE AG) * claim 1; page 5, last paragraph to page 6, line 18; page 11, lines 15-19; pages 15-17 *	1,3,4, 11,12	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D
A,D	FR-A-2 566 774 (EGIS GYOGYZERGYAR) * claim 5; page 20, table V *	13	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	20 MARCH 1992	CHRISTIAN HASS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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